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A NUMERICAL APPROACH TO THE CONVOLUTION EQUATIONS OF A MATHEMATICAL MODEL OF CHEMOTHERAPY

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SANTA MONICA • CALIFORNIA

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PREFACE

The physical assumption of laminar flow in the large blood vessels further complicates the mathematical model of drug distribution in the body by introducing convolution terms which are difficult computationally. This Memorandum tackles the new equations of the chemotherapy model and presents a method suitable for programming this model as well as other biological systems involving equations of this type.

SUMMARY

The new model of drug distribution in the body incorporates the exchange between the stationary and flowing phases in the large blood vessels. This introduces computationally difficult convolution terms. The method of differential approximation applied to the convolution equations reduces this model to a system of differential-difference equations which can be solved computationally.

CONTENTS

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1. INTRODUCTION

Mathematical models of drug distribution presented in previous papers [1 – 5] involved the physical assumption of volume displacement flow in the large blood vessels and led to a system of differential–difference equations with time delays arising from the non–zero recirculation time of the blood. These time lags together with the parameters involving the heart as a mixing pot compensated for the assumption of "slug" flow with no mixing in the arteries and veins. This model initiated continuing research on the numerical solution of differential–difference equations (see [7,8,9]).

The work of Cooper and Jacquez incorporates the exchange between the stationary and flowing phases in the large blood vessels using some results of Landahl (see [6],[10]). These assumptions lead to a set of differential equations together with some equations containing convolution terms, an additional complication. The problem of obtaining a numerical solution of equations of this nature has in turn stimulated considerable research on various approximation techniques since convolution terms introduce significant time and storage problems. We shall apply here some recent results on differential approximation (see [11]) to the equations of our model and obtain thereby a new set of differential–difference equations which can be solved by means of the

techniques described in the foregoing references. Further details will be presented in a subsequent paper describing the digital computer program.

2. THE EQUATIONS OF THE MODEL

The equations (see [4],[10]) of our two organ model consist of a set of 16 first order differential equations for the functions $u_{j,m}$, v_j, w_j, z_j, $j=1, 2$, $m=2, 3, \ldots, 6$, and the following 3 convolution equations for the functions $u_{1,1}$, $u_{2,1}$, U_L (unless otherwise specified these functions are functions of t):

$$(1) \qquad u'_{1,1} = H_1 + d_1 \int_0^{t-s} U_L(q)G(t-s-q)dq$$

$$(2) \qquad u'_{2,1} = H_2 + d_2 \int_0^{t-s} U_L(q)G(t-s-q)dq$$

$$(3) \qquad U'_L = H_3 + d_3 \int_0^{t-s} u_{1,6}(q)G(t-s-q)dq$$

$$+ d_4 \int_0^{t-s} u_{2,6}(q)G(t-s-q)dq \ .$$

Here $s = \ell v_f/c$, with time dimension,

$$a = e^{-(\kappa\ell/c)}, \quad b = \kappa^2\ell/v_s c, \quad h = \kappa/v_s$$

$$d_1 = g_1 a(nc_1/R_{p1}), \quad d_2 = g_1 a(nc_2/R_{p2}), \quad d_3 = g_1 ac_1, \quad d_4 = g_1 ac_2,$$

$$H_1 = \frac{nc_1}{R_{p1}}\left[g_1 a\ U_L(t-s) - u_{1,1}\right] - \frac{k_e A_{e1}}{R_{p1}}\left[u_{1,1} - v_1\right]$$

$$H_2 = \frac{nc_2}{R_{p2}}\left[f_2(t) + g_1 a\ U_L(t-s) - u_{2,1}\right] - \frac{k_e A_{e2}}{R_{p2}}\left[u_{2,1} - v_2\right]$$

$$H_3 = \frac{c}{V^*}\left[g_1 a \frac{c_1 u_{1,6}(t-s) + c_2 u_{2,6}(t-s)}{c} + g_2 f_1(t) - U_L\right]$$

$$G(x) = e^{-hx}\frac{d(I_0(2\sqrt{bx}))}{dx} = e^{-hx}\sqrt{b/x}\ I_1(2\sqrt{bx})$$

where I_1 is the 1-st modified Bessel function of the first kind. It should be pointed out that the 19 functions in this system of equations are zero for $t \leq 0$.

For simplicity the model assumes the same length ℓ for the large blood vessels leading to and from organs 1 and 2. This leads to differential-difference equations involving one time lag, s. We can, however, handle different commensurate time lags (see [12]). This, of course, increases time and storage requirements.

We will proceed to replace each of the three convolution equations by a set of differential-difference equations using a procedure described in the sections that follow.

3. DIFFERENTIAL APPROXIMATION

The method of differential approximation (see [11]) permits us to obtain a set of coefficients, a_i, $i = 1,\ldots,N$, so that $G^{(N)}(x) + \sum_{i=1}^{N} a_i G^{(N-i)}(x) \cong 0$, in the mean square sense. We proceed as follows.

The modified Bessel function of the first kind satisfies the second order differential equation

$$I_1''(z) + \frac{1}{z} I_1'(z) - (1 + \frac{1}{z^2}) I_1(z) = 0 .$$

From this it follows that

$$xG''(x) + G'(x)(2hx+2) + G(x)(h^2x+2h-b) = 0 .$$

By repeated differentiation we obtain

$$xG^{(N+1)} + (2hx+N+1)G^{(N)} + (2hN+h^2x-b)G^{(N-1)}$$
$$+ h^2(N-1)G^{(N-2)} = 0 .$$

Let $G_i(x) = G^{(i)}(x)$ and consider the N+1 differential equations

$$(4) \qquad \begin{cases} \dfrac{dG_i}{dx} = G_{i+1} , & i = 0, 1, \ldots, N-1 \\ \dfrac{dG_N}{dx} = \dfrac{1}{x} \left\{ (2hx+N+1)G_N + (2hN+h^2x-b)G_{N-1} + h^2(N-1)G_{N-2} \right\} \end{cases}$$

The initial conditions $G_i(0)$ can be obtained from the known series expansion for $I_1(x)$, namely

$$G(x) = e^{-hx}\left(b + \frac{b^2x}{2} + \frac{b^3x^2}{3(2!)^2} + \ldots + \frac{b^{(n+1)}x^n}{(n+1)(n!)^2} + \ldots \right).$$

We wish to determine the coefficients a_i so that over a suitable range T we obtain the minimum

$$M = \min_{a_i} \int_0^T \left[G_N(x) + \sum_{i=1}^{N} a_i G_{(N-i)} \right]^2 dx \ .$$

Setting the partial derivatives of M with respect to a_i equal to zero, we obtain the linear system

$$\sum_{j=1}^{N} a_j \int_0^T G_{N-i} G_{N-j} \ dx = -\int_0^T G_{N-i} G_N \ , \qquad i = 1, N \ .$$

Let

$$P_{k,q} = \int_0^T G_k G_q dx \ , \qquad k, q = 0, \ldots, N-1$$

$$Q_k = \int_0^T G_k G_N dx \ , \qquad k = 0, \ldots, N-1 .$$

To the set of equations (4), add the following differential equations

$$(5) \quad \begin{cases} \dfrac{dP_{k,q}}{dx} = G_k G_q \ , & P_{k,q}(0) = 0, \ k,q = 0, , \ldots, N-1 \\[2ex] \dfrac{dQ_k}{dx} = - G_k G_N \ , & Q_k(0) = 0, \ k = 0, \ \ldots, \ N-1 \ . \end{cases}$$

Integrating the combined set of equations (4) and (5) and taking the final values of $P_{k,q}$ and Q_k at $x = T$, we solve the following system of N linear equations in N unknowns a_{N-q}, $q = 0, \ldots, N-1$,

$$\sum_{q=0}^{N-1} a_{N-q} P_{k,q}(T) = Q_k(T), \qquad k = 0, \ldots, N-1 .$$

The solution gives us $a_N, a_{N-1}, \ldots, a_1$.

4. REDUCTION TO A SYSTEM OF DIFFERENTIAL-DIFFERENCE EQUATIONS

For simplicity of presentation, let us assume $N = 3$ for the order of the differential approximation. Let us define

$$X(t) = \int_0^t U_L(q)G(t-q)dq$$

$$Y(t) = \int_0^t u_{1,6}(q)G(t-q)dq$$

$$Z(t) = \int_0^t u_{2,6}(q)G(t-q)dq ,$$

and

$$X_i = X^{(i)}, \quad Y_i = Y^{(i)}, \quad Z_i = Z^{(i)} .$$

The 3 convolution equations become

$$(6) \qquad u_{1,1}' = H_1 + d_1 X(t-s)$$

$$(7) \qquad u_{2,1}' = H_2 + d_2 X(t-s)$$

$$(8) \qquad U_L' = H_3 + d_3 Y(t-s) + d_4 Z(t-s)$$

To these equations adjoin the following set:

$$(9) \qquad \begin{cases} X' = X_1, & X(0) = 0 \\ X_1' = X_2, & X_1(0) = 0 \\ X_2' = H_4(X, X_1, X_2, U_L, U_L', U_L''), & X_2(0) = 0 \\ Y' = Y_1, & Y(0) = 0 \\ Y_1' = Y_2, & Y_1(0) = 0 \\ Y_2' = H_4(Y, Y_1, Y_2, u_{1,6}, u_{1,6}', u_{1,6}''), & Y_2(0) = 0 \\ Z' = Z_1, & Z(0) = 0 \\ Z_1' = Z_2, & Z_1(0) = 0 \\ Z_2' = H_4(Z, Z_1, Z_2, u_{2,6}, u_{2,6}', u_{2,6}''), & Z_2(0) = 0\ . \end{cases}$$

The function H_4 and the initial conditions are obtained as follows: Illustrating with $X(t)$, by using Leibniz's rule repeatedly, we get

$$(10) \qquad X'(t) = G(0)U_L''(t) + \int_0^t G'(t-q)U_L(q)dq$$

$$(11) \qquad X''(t) = G(0)U_L'(t) + G'(0)U_L(t) + \int_0^t G''(t-q)U_L(q)dq$$

$$X'''(t) = G(0)U_L''(t) + G'(0)U_L'(t) + G''(0)U_L(t) + \int_0^t G'''(t-q)U_L(q)dq \; . \tag{12}$$

Combining these together with the 3 coefficients a_i of our differential approximation, we obtain

$$X''' + a_1X'' + a_2X' + a_3X = G(0)U_L''(t) + G'(0)U_L'(t) + G''(0)U_L(t)$$

$$+ a_1(G(0)U_L'(t) + G'(0)U_L(t)) + a_2G(0)U_L(t)$$

$$+ \int U_L(q)(G'''(t-q) + a_1G''(t-q) + a_2G'(t-q) + a_3G(t-q))dq \; .$$

By a change of variable and the result of Sec. 3, the integrand in the last term vanishes. The function H_4 by virtue of (13) is given by

$$H_4(X, X_1, X_2, U_L, U_L', U_L'') = -a_3X - a_2X_1 - a_1X_2$$

$$+ \left[G''(0) + a_1G'(0) + a_2G(0)\right]U_L + \left[G'(0) + a_1G(0)\right]U_L' + G(0)U_L''$$

By going back to the equations of the model (see [4],[10]) the derivative terms $U_L', U_L'', u_{j,6}', u_{j,6}''$, $j=1,2$, in the function H_4, can be expressed in terms of the original functions of our set of 28 differential-difference equations, for a

two organ model with a third order differential approximation for $G(x)$. Differential approximation of order k involves a system of $19 + 3k$ equations.

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